REMARKS

Claim Rejections – 35 USC §103

Claims 1-22 were rejected under 35 U.S.C. 103(a) as being unpatentable over Greef, U.S. Patent Application Publication No. US 2002/0053545, filed August 2, 2001, and published May 9, 2002, in view of Desmartis et al., European Patent Application Publication EP 0 969 283 A1, published May 1, 2000.

The present application claims priority from two provisional patent applications, U.S. Provisional Application No. 60/253,178, filed November 27, 2000 (the '178 application), and U.S. Provisional Application No. 60/314,996, filed August 24, 2001. Under 35 U.S.C. 102(e) as amended by H.R. 2215, Greef has a 102(e) prior art date of its earliest effective U.S. filing date, August 2, 2001, and is therefore not prior art for claims that are entitled to the filing date of the '178 application.

The '178 application discusses the use of "a windowed-median-filter algorithm (a nonlinear filter) to remove noise" from LC-MS data (p. 14, first full paragraph, and Figure 3). For the convenience of the Examiner, relevant portions of the '178 application are provided in the Appendix to this Amendment and Remarks document. Applicant submits that at least claims 1-4, 10-15, and 21-22 are entitled to claim priority from the '178 application. As such, Greef is not prior art for these claims, and rejections of these claims should be removed.

Regarding the remaining claims, 5-9 and 16-20, Applicant submits that, as set forth below, the prior art references do not teach or suggest all of the claim elements. As such, a *prima facie* case of obviousness cannot be established, and the rejections should be withdrawn.

Desmartis et al. is directed to a method for processing measuring values, such as chromatograms, by applying a morphological filter. Using structural elements of the filter, the signal is decomposed into segments, allowing removal of high-frequency noise and estimation of peak areas.

The Examiner relies on the Desmartis et al. reference as disclosing the use of a median filter to remove noise data from chromatograms, as recited in claim 1. However, the entire description in Desmartis et al. is of morphological filters; a median filter is mentioned briefly in only four locations: the abstract (part (a), third line), summary (col. 1, lines 46-47 and 58), detailed description (col. 9, line 13), and claim 1 (col. 9, line 31). Importantly, there is no description of how to implement a median filter, only the possibility that it can be employed. The detailed description says only that "[i]nstead of a morphological filter, a related but non-morphological filter, such as a median filter, could be used" (col. 9, lines 11-13).

Regarding claims 5 and 16, neither Desmartis et al. nor Greef discloses a modified median filter. The Examiner points to a section of Desmartis et al. that teaches that "[t]he mentioned morphological filters offer a great versatility. Due to the possibility to choose the reference form, i.e., the structuring element, … one can customize the filters to treat a wide range of problems" (col. 3, lines 11-16). The Examiner then argues that "since the median filter can be substituted for the morphological filter, it too can be modified."

The Examiner appears to have misinterpreted the term "modified median filter" as referring to a median filter that is customized by choosing certain parameters. A modified median filter, as known in the art, is a median filter that has a modification to its structure, typically to provide increased flexibility, and not simply to its parameter. See, e.g., R.A. Haddad and T.W. Parsons, *Digital Signal Processing: Theory, Applications, and Hardware*, W.H. Freeman and Company, 1991. As described therein, modified median filters can employ a variety of modifications; for example, they may filter recursively or use an order statistic other than the median, a linear combination of order statistics, or a linear combination of points within a neighborhood of the median.

A standard median filter has a single parameter, the window size, and varying that parameter does not change the form of the filter or produce a modified median filter. The reference in Desmartis et al. to choosing the structural reference form of the

morphological filter is not relevant to a median filter, which does not have a structural reference form.

Thus neither Desmartis et al. nor Greef discloses a modified median filter. Since not all claim limitations are disclosed in the references, a *prima facie* case of obviousness cannot be established, and Applicant requests the removal of the rejections of claims 5 and 16.

Claims 6 and 17 have been canceled and their dependent claims, 7-9 and 18-20, amended to depend from claims 1 and 12, respectively. Claims 7-9 and 18-20 include the limitations of selecting a parameter of a median filter in dependence on various factors. Neither reference discloses or suggests the selection of a parameter of a median filter. Desmartis et al. discusses parameters of a morphological filter—minimal height, minimal width, and maximal width (col. 2, lines 25-26)—none of which is relevant to a median filter. The only argument the Examiner provides for the suggestion of the claim limitations in Desmartis et al. is that "it would have been obvious … to select various parameters of the median filter," with a motivation that "the median filter can be customized to treat a wide range of problems." As mentioned above, there is no reference in Desmartis et al. to the parameter of a median filter or the customization of the median filter, and so there is clearly no teaching or suggestion of the selection of such a parameter.

Regarding the specific factors—a scan rate of mass spectrometry, subsequent data analysis, and peak selection, respectively—none of these is taught or suggested in the references as factors on which parameter selection depends. Applicant respectfully points out to the Examiner that claims 7-9 and 18-20 do not simply recite parameter selection and various factors; rather, they recite parameter selection <u>in dependence on</u> those factors. Thus for a valid rejection, the reference must explicitly describe this connection, not simply disclose the features independently without providing any link between them.

Not only does Desmartis et al. fail to mention any parameters of a median filter, much less how to select them, it also provides little guidance for selecting even the morphological

filter parameters. For example, "the minimal height parameter ... can typically be chosen such that it is greater than the noise level, but smaller than the smallest peak" (col. 7, lines 12-15). Additionally, "the minimal peak width is determined by the resolution of the chromatographic apparatus and the maximal peak width is a parameter to be chosen as being smaller than the wander and baseline variations" (col. 7, lines 54-58). In all cases, the parameters of the morphological filter are chosen in dependence on characteristics of the raw data, not on any of the limitations of claims 7-9 and 18-20.

Regarding claims 7 and 18, which recite selecting the parameter in dependence on a mass spectrometry scan rate, Desmartis et al. makes no reference to mass spectrometry, while Greef makes no reference to a median filter. There is clearly no linkage in either reference or in the combination of references, therefore, to selecting a median filter parameter in dependence on a mass spectrometry scan rate. With respect to claims 8-9 and 19-20, there is no disclosure of parameters chosen based on subsequent data analysis, but only on characteristics in place before the filter is applied. Regarding claims 9 and 20, the Examiner maintains that Desmartis et al. teaches peak detection as a subsequent data analysis. Again, this is not relevant to the claims, which recite not simply that subsequent data analysis includes peak picking, but that the median filter parameter is chosen in dependence on the peak picking.

Applicant submits that because the references neither teach nor suggest all of the limitations of claims 7-9 and 18-20, the rejections are unsupported by the art and should be withdrawn.

Thus, Applicant requests that the Examiner reconsider the application and issue a Notice of Allowance in the next Office Action. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefor to deposit account No. 19-5117, if not otherwise specifically requested.

The undersigned hereby authorizes the charge of any fess created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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APPENDIX

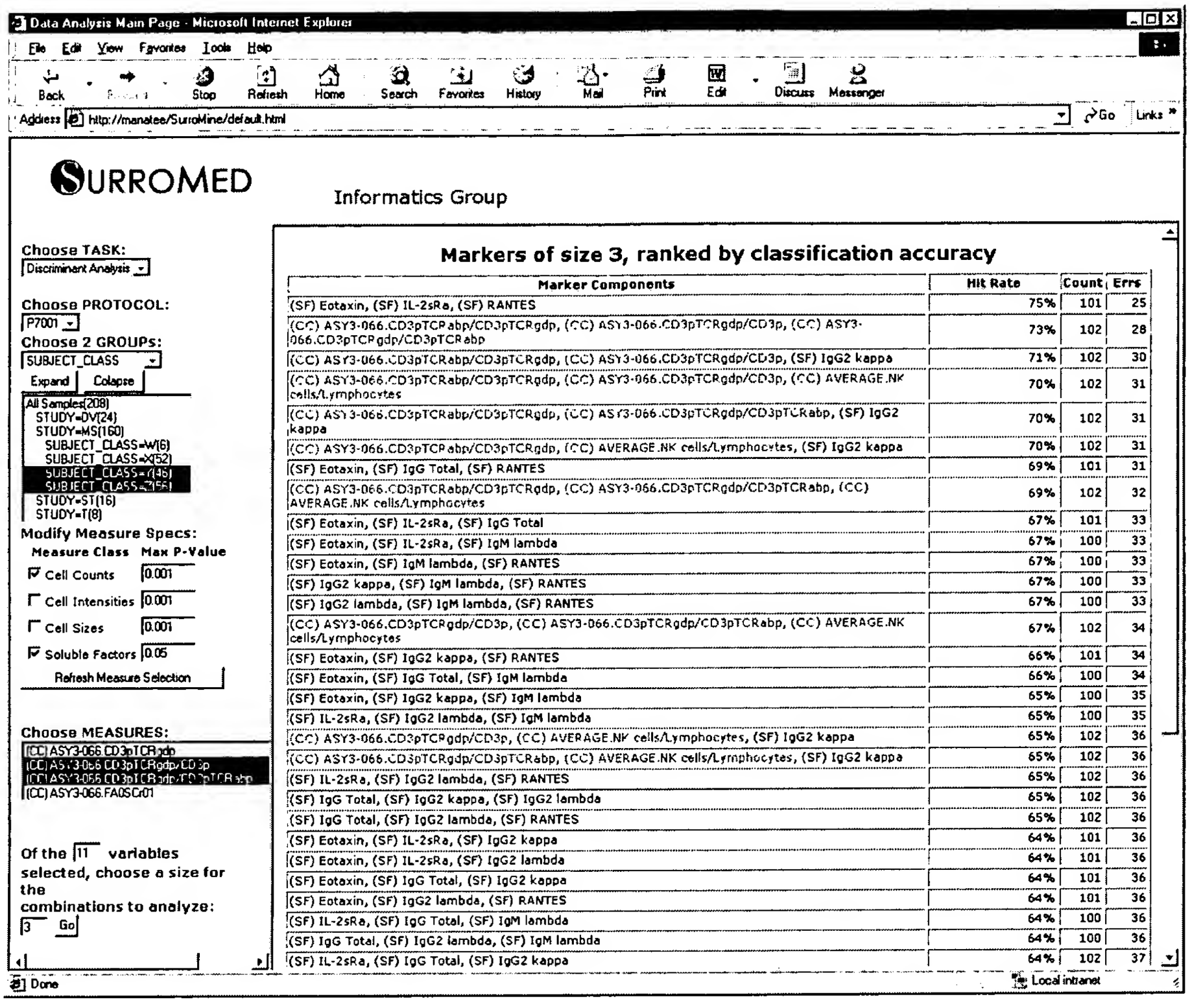

Figure 2: The interface of our Discriminant analysis tool used for mining broad bioanalysis data sets for biomarkers.

Mass Spectrometry data analysis informatics

Mass spectrometry is the newest addition to SurroMed's toolbox for the discovery of novel biomarkers through differential protein and organic molecule phenotyping. Our rationale for choosing mass spectrometry as a critical detection element for differential molecular phenotyping is predicated on its applicability to gather information for both high and low molecular weight species. Indeed, it is the only technique capable of both furnishing molecular identification of peptide fragments associated with large proteins and molecular weight/identification of molecules in the 100-500 atomic mass unit (amu) range. Moreover, insofar as several masses can be identified simultaneously, mass spectrometry is an intrinsically multiplexed detection technique. The multiplexed nature of mass spectrometry makes it a rich source of information, yet presents many technical challenges in terms of establishing a

bioinformatics infrastructure similar to that in place for cytometry and immunoassays. We have begun preliminary work in the areas of collecting and processing mass spectral data suitable for storage and mining in our central Oracle database.

SurroMed has acquired three mass spectrometer instruments with plans to purchase a fourth instrument in the near future. These consist of: a Finnigan LCQ-DECA ion trap-based electrospray (ESI) instrument; a Kodiak 1200 triple quad electron ionization (EI) and chemical ionization (CI) mass spectrometer from Bear Instruments; and a Voyager DE-PRO matrix-assisted laser desorption/ionization (MALDI) instrument from PerSeptive Biosystems.

Mass spectrometry file formats from different instruments are not standardized or publicized, as described in *Section B*. Our initial endeavor was to find a file format that could support all the modes of operations from each manufacturer's instrument. Bear Instruments' mass spectral file format was found to be flexible enough to support data produced by various modes of operation from the other two instruments, and we have partnered with them to support assay development and to provide some software development resources. Through our partnership with Bear and using component object modules (COMs) provided by Finnigan, we have developed C++ software to convert our Finnigan and PerSeptive data formats to the Bear format.

A typical mass spectrometer run of one hour in length on the ESI instrument can generate extremely large data files (typically 15MB to 80MB). From both a storage and mining perspective, this data needs to be reduced in such a manner as to retain its information content, yet discard noise. We have begun investigating algorithms for noise reduction as well as peak extraction methods including Biller-Biemann (BB) and extensions (3-4), the Windowed Mass Selection Method (5), Singular Value Decomposition (SVD) (6), the Component Detection Algorithm (CODA) (7), the Sequential-Paired Covariance (SPC) (8), Higher Order Sequential Paired Covariance (HO-SPC) (9), Backfolding (10), and Principal Component Analysis (PCA) (11). Using Mathwork's MATLAB, a high-level numerical language, these algorithms have been implemented and tested. These traditional methods for processing LC-MS data are designed for small molecule mixtures in which the level of analytes is relatively high, the noise being dominated by contributions from the LC mobile phase. It is desirable to identify individual components on the basis of their mass spectra including ions arising from fragmentation of their parent ion. These methods improve the appearance of the total ion current (TIC) plot by

removing mass chromatograms containing only noise and mass chromatograms with high background (i.e., CODA) or by sharpening individual component peaks (i.e., Backfolding). Component mass spectra are then identified from TIC peaks by calculating precise elution times for each ion peak (4) and finding components that co-elute (i.e., Biller-Biemann). In all of these cases, we propose that resultant pre-processed component mass spectra be stored in a database for future mining.

A problem with the above methods is the fact that they assume the noise in a spectrum is normally distributed. Our experience has shown that, in fact, the noise spectrum is non-normally distributed and therefore, we have developed a windowed-median-filter algorithm (a nonlinear filter) to remove noise. Initially results are quite promising (Figure 3) and we plan on continuing to explore this issue.

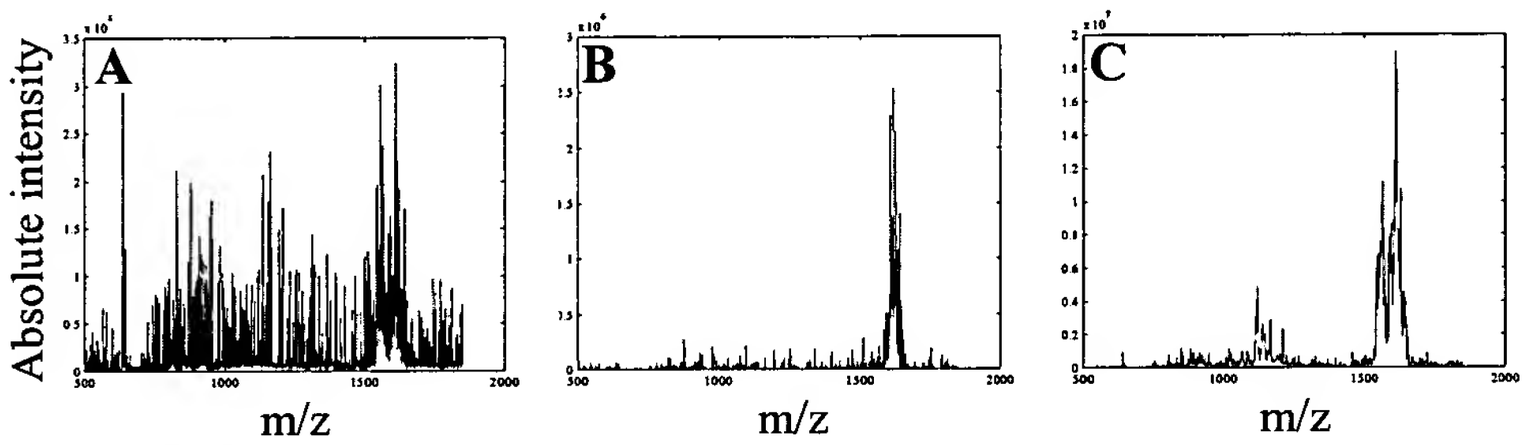

Figure 3: Preliminary results on preprocessing electrospray ionization (ESI) mass specrtral data. (A) represents the original total ion current (TIC). (B) represents CODA-(Similarity index is 0.8, averaging window is 5 points) processed data and (C) demonstrates that application of a custom median filter before CODA processing brings out suppressed components near m/z = 1150.

One key component of differential phenotyping using mass spectral data will be the algorithm chosen to recognize differences in mass spectra between biosamples drawn from different patients. Clustering algorithms, including principal component analysis (PCA) (12) and neural networks (13) (optimal for nonlinear models) hold promise. We have purchased a software package, HighChem Mass Frontier™, that supports principal component analysis of single mass spectra. While our needs will require a package that can analyze a complete mass spectrogram, this package offers some insight into the capabilities of this algorithm.

Nanobar Code Identification Tag separations analyzed with mass spectrometry